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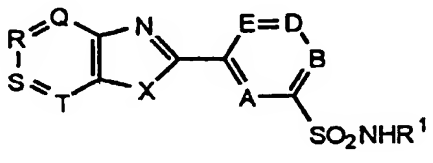
(54) Title: HETEROBIARYLSULPHONAMIDES AND THEIR USE AS PDE 7 INHIBITORS



(1)

(57) Abstract: Compounds of formula (1) are described, wherein R^1 represents an aryl or heteroaryl group; A, B, D and E, which may be the same or different, each represents a nitrogen atom or a $C(R^2)$ group [in which R^2 is a hydrogen or halogen atom or an alkyl, haloalkyl, alkoxy, haloalkoxy, hydroxy, $-NO_2$ or -CN group] provided that two or more of A, B, D and E are $C(R^2)$ groups; X represents an oxygen or sulphur atom or a $N(R^3)$ group in which R^3 is a hydrogen atom or an alkyl group; Q, R, S and T, which may be the same or different each represents a nitrogen atom or a group $C(R^4)$ [in which R^4 is an atom or group $-L^1(Alk^1)_rL^2(R^5)_s$], provided that two or more of Q, R, S and T are $C(R^4)$ groups. The compounds are potent and selective inhibitors of the enzyme phosphodiesterase 7 and are of use in the treatment of autoimmune and other diseases in which inhibition of the enzyme can have a beneficial effect.

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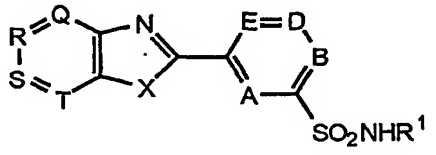
HETEROBIARYLSULPHONAMIDES AND THEIR USE AS PDE 7 INHIBITORS

This invention relates to a series of heterobiarylsulphonamides, to processes for their preparation, to pharmaceutical compositions containing them, and to their use in medicine.

The cyclic nucleotides cAMP and cGMP are known to be responsible for the regulation of a variety of intracellular processes. The levels of these nucleotides are modulated by the stimulation of adenylate or guanylate cyclases and by the activity of phosphodiesterase enzymes. Phosphodiesterases (PDEs) specifically convert cyclic nucleotides to inactive analogues. Eleven PDE gene familes have been identified to date, based on substrate specificity and regulatory characteristics. PDE7 is a low K_M cAMP specific enzyme which is insensitive to the standard PDE4 inhibitor, rolipram. PDE7 is thought to play an important role in T cell activation [Beavo *et al*,, Science (1999), 283: 848], which implies that inhibitors of PDE7 should have benefit in T cell mediated diseases. In addition, PDE7 has been detected in airway epithelial cells [Barnes *et al*, Am. J. Respir. Cell Mol. Biol. (1999) 20: 292] so inhibitors should be beneficial in diseases of the airway.

We have now found a series of heterobiarylsulphonamides which are potent and selective inhibitors of PDE7. The compounds are thus of use in the prophylaxis and treatment of diseases in which inhibition of PDE7 can have a therapeutic benefit.

Thus according to one aspect of the invention we provide a compound of formula (1):



(1)

wherein

R^1 represents an aryl or heteroaryl group;
A, B, D and E, which may be the same or different, each represents a nitrogen atom or a $C(R^2)$ group [in which R^2 is a hydrogen or halogen atom or an alkyl, haloalkyl, alkoxy, haloalkoxy, hydroxy, $-NO_2$ or -CN group] provided that two or more of A, B, D and E are $C(R^2)$ groups;
X represents an oxygen or sulphur atom or a $N(R^3)$ group in which R^3 is a hydrogen atom or an alkyl group;
Q, R, S and T, which may be the same or different each represents a nitrogen atom or a group $C(R^4)$ [in which R^4 is an atom or group $-L^1(Alk^1)_rL^2(R^5)_s$ in which L^1 and L^2, which may be the same or different, is each a covalent bond or a linker atom or group, r is zero or the integer 1, Alk^1 is an aliphatic or heteroaliphatic chain, s is an integer 1, 2 or 3 and R^5 is a hydrogen or halogen atom or a group selected from alkyl, $-OR^6$ [where R^6 is a hydrogen atom or an optionally substituted alkyl group], $-SR^6$, $-NR^6R^7$ [where R^7 is as just defined for R^6 and may be the same or different], $-NO_2$, -CN, $-CO_2R^6$, $-SO_3H$, $-S(O)R^6$, $-SO_2R^6$, $-OCO_2R^6$, $-CONR^6R^7$, $OCONR^6R^7$, $-CSNR^7R^7$, $-OCR^6$, $-OCOR^6$, $-N(R^6)COR^7$, $-N(R^6)CSR^7$, $S(O)NR^6R^7$, $-SO_2NR^6R^7$, $-N(R^6)SO_2R^7$,$-N(R^6)CON(R^7)(R^8)$ [where R^8 is a hydrogen atom or an optionally substituted alkyl group], $-N(R^6)CSN(R^7)R^8)$, $-N(R^6)SO_2N(R^7)(R^8)$, $-C(R^6)=NO(R^7)$,cycloaliphatic, heterocycloaliphatic, aryl or heteroaryl group] provided that two or more of Q, R, S and T are $C(R^4)$ groups;
and the salts, solvates, hydrates and N-oxides thereof.

Aryl groups represented by the group R^1 in compounds of formula (1) include for example mono- or bicyclic C_{6-12} optionally substituted aromatic groups, for example optionally substituted phenyl, 1– or 2–naphthyl, or indenyl groups.

Heteroaryl groups represented by R^1 include for example C_{1-9} optionally substituted heteroaromatic groups containing for example one, two, three or four heteroatoms selected from oxygen, sulphur or nitrogen atoms. In general, the heteroaromatic groups may be for example monocyclic or bicyclic heteroaromatic groups. Monocyclic heteroaromatic groups include for example five- or six-membered heteroaromatic groups containing one, two, three or four heteroatoms selected from oxygen,

sulphur or nitrogen atoms. Bicyclic heteroaromatic groups include for example nine- to thirteen-membered heteroaromatic groups containing one, two or more heteroatoms selected from oxygen, sulphur or nitrogen atoms.

Particular examples of heteroaryl groups represented by R^1 include optionally substituted pyrrolyl, furyl, thienyl, imidazolyl, N-methylimidazolyl, N-ethylimidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,3,4-thiadiazole, pyridyl, pyrimidinyl, pyridazinyl, pyrazinyl, 1,3,5-triazinyl, 1,2,4-triazinyl, 1,2,3-triazinyl, benzofuryl, isobenzofuryl, benzothienyl, benzotriazolyl, isobenzothienyl, indolyl, isoindolyl, benzimidazolyl, imidazo[1,2-a]pyridyl, benzothiazolyl, benzoxazolyl, quinazolinyl, naphthyridinyl, pyrido[3,4-b]pyridyl, pyrido[3,2-b]pyridyl, pyrido[4,3-b]pyridyl, quinolinyl, isoquinolinyl, tetrazolyl, 5,6,7,8-tetrahydroquinolinyl and 5,6,7,8-tetrahydroisoquinolinyl.

The aryl or heteroaryl groups represented by R^1 may be attached to the -NH- group of the remainder of the molecule of formula (1) through any available ring carbon atom as appropriate.

Optional substituents present on the aryl or heteroaryl groups represented by R^1 include one, two, three or more groups, each represented by the group R^{4a}, where R^{4a} is a $-L^1(Alk^1)_rL^2(R^5)_s$ group as generally defined above and more specifically described hereinafter provided that $-L^1(Alk^1)_rL^2(R^5)_s$ does not represent -H. Where more than one R^{4a} substituent is present, these may be the same or different.

When in the compounds of formula (1) L^1 and/or L^2 is present as a linker atom or group in a substituent R^4 and/or R^{4a}, each L^1 and/or L^2 group may be for example an -O- or -S- atom or a -C(O)-, -C(S)-, -S(O)-, $-S(O)_2$-, $-N(R^9)$- [where R^9 is a hydrogen atom or a C_{1-6} alkyl, e.g. methyl or ethyl, group], $-CON(R^9)$-, $-OC(O)N(R^9)$-, $-CSN(R^9)$-, $-N(R^9)CO$-, $-N(R^9)C(O)O$-, $-N(R^9)CS$-, $-SON(R^9)$, $-SO_2N(R^9)$, $-N(R^9)SO_2$-, $-N(R^9)CON(R^9)$-, $-N(R^9)CSN(R^9)$-, $-N(R^9)SON(R^9)$- or $-N(R^9)SO_2N(R^9)$ -group. Where the

linker group contains two R^9 substituents these may be the same or different.

When Alk^1 is present in the compounds of the invention it may be a C_{1-10} aliphatic chain, for example a straight or branched chain C_{1-6}alkylene, e.g. C_{1-3}alkylene, C_{2-6}alkenylene, e.g. C_{2-4}alkenylene, or C_{2-6}alkynylene, e.g. C_{2-4} alkynylene chain. Each of said chains may be optionally interrupted by one or two heteroatoms or heteroatom-containing groups represented by L^3 [where L^3 is an atom or group as just described for L^1], to form an Alk^1 heteroaliphatic chain.

Particular examples of aliphatic chains represented by Alk^1 include $-CH_2-$, $-CH_2CH_2-$, $-(CH_2)_2CH_2-$, $-CH(CH_3)CH_2-$, $-(CH_2)_3CH_2-$, $-CH(CH_3)CH_2CH_2-$, $-CH_2CH(CH_3)CH_2-$, $-C(CH_3)_2CH_2-(CH_2)_4CH_2-$, $-(CH_2)_5CH_2-$, $-CHCH-$, $-CHCHCH_2-$, $-CH_2CHCH_2-$, $-CHCH(CH_2)_2-$, $-CH_2CHCHCH_2-$, $-(CH_2)_2CHCH_2$, $-CC-$, $-CCCH_2-$, $-CH_2CC-$, $-CC(CH_2)_2-$, $-CH_2CCCH_2-$, or $-(CH_2)_2CC-$ chains. Where appropriate each of said groups may be optionally interrupted by one or two atoms and/or groups L^3 to form a heteroaliphatic chain.

When the substituent R^5 is present in compounds of formula (1) as a halogen atom it may be for example a fluorine, chlorine, bromine or iodine atom.

Alkyl groups represented by the group R^5 include straight or branched C_{1-6}alkyl groups, e.g. C_{1-3}alkyl groups such as methyl or ethyl groups.

Optionally substituted alkyl groups represented by R^6, R^7 and/or R^8 in compounds of the invention include those alkyl groups just mentioned for R^5 optionally substituted by one, two or three substituents selected from halogen atoms, e.g. fluorine, chlorine, bromine or iodine atoms, or hydroxy or C_{1-3}alkoxy e.g. methoxy or ethoxy groups.

When R^5 is present in compounds of formula (1) as a cycloaliphatic group it may be an optionally substituted C_{3-10} cycloaliphatic group. Particular

examples include optionally substituted C_{3-10}cycloalkyl, e.g. C_{3-7}cycloalkyl or C_{3-10}cycloalkenyl e.g. C_{3-7} cycloalkenyl groups.

Heterocycloaliphatic groups represented by R^5 include the cycloaliphatic groups just described for R^5 but with each group additionally containing one, two, three or four heteroatoms or heteroatom-containing groups represented by L^4, where L^4 is an atom or group as described above for L^1.

Particular examples of R^5 cycloaliphatic and heterocycloaliphatic groups include optionally substituted cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, 2-cyclobuten-1-yl, 2-cyclopenten-1-yl, 3-cyclopenten-1-yl, 2,4-cyclopentadien-1-yl, 3,5,-cyclohexadien-1-yl, pyrroline, e.g. 2- or 3-pyrrolinyl, pyrrolidinyl, dioxolanyl, e.g. 1,3-dioxolanyl, imidazolinyl, e.g. 2-imidazolinyl, imidazolidinyl, pyrazolinyl, e.g. 2-pyrazolinyl, pyrazolidinyl, pyranyl, e.g. 2- or 4-pyranyl, piperidinyl, 1,4-dioxanyl, morpholinyl, 1,4-dithianyl, thiomorpholinyl, piperazinyl, homopiperazinyl, 1,3,5-trithianyl, oxazinyl, e.g. 2H-1,3-, 6H-1,3-, 6H-1,2-, 2H-1,2- or 4H-1,4- oxazinyl, 1,2,5-oxathiazinyl, isoxazinyl, e.g. o- or p-isoxazinyl, oxathiazinyl, e.g. 1,2,5 or 1,2,6-oxathiazinyl, or 1,3,5,2-oxadiazinyl groups.

Optional substituents which may be present on R^5 cycloaliphatic and heterocycloaliphatic groups include one, two, three or more substituents selected from halogen atoms, e.g. fluorine, chlorine, bromine or iodine atoms, C_{1-6}alkyl, e.g. methyl or ethyl, C_{1-6}alkoxy, e.g. methoxy or ethoxy or hydroxyl groups. The heterocycloaliphatic groups may be attached to the remainder of the molecule of formula (1) through any appropriate ring carbon or heteroatom.

Aryl or heteroaryl groups represented by the group R^5 include those aryl and heteroaryl groups generally and specifically described herein in relation to the group R^1. Each group may be attached to the remainder of the molecule of formula (1) through any available ring carbon or heteroatom as appropriate.

Where more than one atom or group R^5 is present in $-L^1(Alk^1)_rL^2(R^5)_s$ [i.e. where s is an integer two or three] it is to be understood that each R^5 atom or group may be the same or different and may be attached to the same or different atoms, particularly for example to form groups such as $-Alk^1(R^5)_2$ or $-Alk^1(R^5)_3$.

Particular examples of substituents represented by R^4 (i.e. when it is other than a hydrogen atom) and/or R^{4a} in compounds of the invention include halogen atoms, e.g. fluorine, chlorine, bromine or iodine atoms, or C_{1-6}alkyl, e.g. methyl or ethyl, haloC_{1-6}alkyl, e.g. halomethyl or haloethyl such as difluoromethyl or trifluoromethyl, optionally substituted by hydroxyl, e.g. $-C(OH)(CF_3)_2$, C_{1-6}alkoxy, e.g. methoxy or ethoxy, haloC_{1-6}alkoxy, e.g. halomethoxy or haloethoxy such as difluoromethoxy or trifluoromethoxy, thiol, C_{1-6}alkylthio e.g. methylthio or ethylthio, or $-(Alk^1)_rR^{5a}$ groups in which Alk^1 is a straight or branched C_{1-3}alkylene chain, r is zero or an integer 1 and R^{5a} is a -OH, -SH, $-N(R^6)(R^7)$, -CN, $-CO_2R^6$, $-NO_2$, $-CON(R^6)(R^7)$, $-CSN(R^6)(R^7)$, $-COR^6$, $-N(R^6)COR^7$, $-N(R^6)CSR^7$, $-SO_2R^6$, $-SO_2N(R^6)(R^7)$, $-N(R^6)SO_2R^7$, $-N(R^6)CON(R^7)(R^8)$, $-N(R^6)CSN(R^7)$, $-N(R^6)SO_2N(R^6)(R^7)$, $-C(R^6)=NO(R^7)$ or optionally substituted cyclopentyl, cyclohexyl, cyclopentyloxy, cyclohexyloxy, phenyl, phenoxy or benzyloxy group.

When R^2 is present in compounds of formla (1) as a halogen atom it may be for example a fluorine, chlorine, bromine or iodine atom.

Alkyl groups represented by the groups R^2 and R^3 in compounds of the invention include straight or branched C_{1-6}alkyl groups as described above for the group R^5. Haloalkyl groups represented by R^2 include those alkyl groups just mentioned substituted by one, two or three halogen atoms, e.g. fluorine or chlorine atoms. Particular examples include $-CH_2F$, $-CHF_2$ and $-CF_3$ groups.

Alkoxy groups represented by R^2 include straight or branched C_{1-6}alkoxy groups, e.g. C_{1-3}alkoxy groups such as methoxy or ethoxy groups. Haloalkoxy groups represented by R^2 include those just mentioned alkoxy groups substituted by one, two or three halogen atoms, e.g. fluorine or

chlorine atoms. particular examples include $-OCH_2F$, $-OCHF_2$ and $-OCF_3$ groups.

The presence of certain substituents in the compounds of formula (1) may enable salts of the compounds to be formed. Suitable salts include pharmaceutically acceptable salts, for example acid addition salts derived from inorganic or organic acids, and salts derived from inorganic and organic bases.

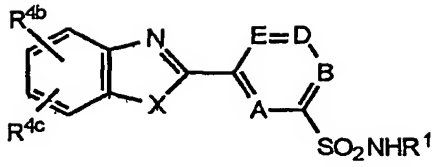
Acid addition salts include hydrochlorides, hydrobromides, hydroiodides, alkylsulphonates, e.g. methanesulphonates, ethanesulphonates, or isothionates, arylsulphonates, e.g. p-toluenesulphonates, besylates or napsylates, phosphates, sulphates, hydrogen sulphates, acetates, trifluoroacetates, propionates, citrates, maleates, fumarates, malonates, succinates, lactates, oxalates, tartrates and benzoates.

Salts derived from inorganic or organic bases include alkali metal salts such as sodium or potassium salts, alkaline earth metal salts such as magnesium or calcium salts, and organic amine salts such as morpholine, piperidine, dimethylamine or diethylamine salts.

Particularly useful salts of compounds according to the invention include pharmaceutically acceptable salts, especially acid addition pharmaceutically acceptable salts.

It will be appreciated that where compounds of formula (1) exist as geometrical isomers and/or exantiomers or diastereomers then the invention extends to all such isomers of the compounds of formula (1), and to mixtures thereof, including racemates.

In the compounds according to the invention, each of Q, R, S and T is preferably a $C(R^4)$ group. One particular group of compounds of this type has the formula (1a):



(1a)

wherein R^{4b} and R^{4c}, which may be the same or different, is each an atom or group $-L^1(Alk^1)_rL^2(R^5)_s$ as generally and particularly defined herein for the group R^4, and X, E, D, B, A and R^1 are as defined for formula (1).

In general in compounds of formulae (1) and (1a) when each of A, B, D and E is a $C(R^2)$ group, R^2 is in particular a hydrogen atom. In one particular preference, each of A, B, D and E is a $C(R^2)$ group in which R^2 is a hydrogen atom.

R^1 in compounds of formulae (1) and (1a) is in particular an optionally substituted phenyl or monocyclic six-membered heteroaromatic group as described herein. Particular examples of such groups include optionally substituted pyridyl or pyrimidinyl groups. R^1 is especially an optionally substituted phenyl group. Optional substituents present on these phenyl and heteroaromatic groups include in particular one or two R^{4a} atoms or substituents as generally and specifically described herein. In compounds of this type R^{4a} is in particular a fluorine, chlorine or bromine atom or a $-CH_3$, $-OCH_3$, $-CF_3$, $-OCHF_2$, $-OCH_3$, $-CN$, $-CO_2H$, $-CO_2CH_3$, $-CO_2CH_2CH_3$, $-NO_2$, $-CONH_2$, $-CONHCH_3$, $-CONHCH_2CH_3$, $-CON(CH_3)_2$ or $-CON(CH_2CH_3)_2$ group.

R^{4b} in compounds of formula (1a) is in particular a hydrogen, fluorine, chlorine or bromine atom or a $-CH_3$, $-OCH_3$, $-CF_3$, $-OCHF_2$, $-OCH_3$, $-CN$, $-CO_2H$, $-CO_2CH_3$, $-CO_2CH_2CH_3$, $-NO_2$, $-CONH_2$, $-CONHCH_3$, $-CONHCH_2CH_3$, $-CON(CH_3)_2$ or $-CON(CH_2CH_3)_2$ group, especially a chlorine atom or a $-NO_2$, $-CO_2H$, $-CO_2CH_3$ or $-CH_3$ group.

In compounds of formula (1a) R^{4a} is in particular a hydrogen atom.

X in compounds of formulae (1) and (1a) is in partiuclar an oxygen atom or a -NH group.

Particularly useful compounds according to the invention include:
N-(4-Chlorophenyl)-3-(7-nitro-1H-benzimidazol-2-yl)benzenesulfonamide;
N-(4-Cyanophenyl)-3-(7-nitro-1H-benzimidazol-2-yl)benzenesulfonamide;
N-(3-Cyanophenyl)-3-(7-nitro-1H-benzimidazol-2-yl)benzenesulfonamide;
N-(3,5-Dichlorophenyl)-3-(7-nitro-1H-benzimidazol-2-yl)benzene-sulfonamide;
N-(4-Bromo-2-chlorophenyl)-3-(7-nitro-1H-benzimidazol-2-yl)benzene-sulfonamide;
N-Ethyl-4-[3-(7-nitro-1H-benzimidazol-2-yl)benzenesulfonylamino]-benzamide;
4-[3-(7-Nitro-1H-benzimidazol-2-yl)benzenesulfonylamino]benzoic acid ethyl ester;
N-(4-Chloro-2-methylphenyl)-3-(7-nitro-1H-benzimidazol-2-yl)benzene-sulfonamide;
2-[3-(2-Chlorophenylsulfamoyl)phenyl]-3H-benzimidazole-4-carboxylic acid methyl ester;
2-[3-(4-Chloro-2-methylphenylsulfamoyl)phenyl]-3H-benzimidazole-4-carboxylic acid;
2-[3-(5-Chloro-1H-benzimidazol-2-yl)benzenesulfonylamino]benzoic acid;
2-[3-(2-Chlorophenylsulfamoyl)phenyl]-3H-benzimidazole-4-carboxylic acid;
2-[3-(4-Chloro-2-methylphenylsulfamoyl)phenyl]benzoxazole-7-carboxylic acid;
2-[3-(5-Chlorobenzoxazol-2-yl)benzenesulfonylamino]benzoic acid;
2-[3-(4-Chloro-2-methylphenylsulfamoyl)phenyl]benzoxazole-4-carboxylic acid;
N-(4-Chloro-2-methylphenyl)-3-(4-nitrobenzoxazol-2-yl)benzene-sulfonamide;
N-(4-Bromophenyl)-3-(4-methylbenzoxazol-2-yl)benzenesulfonamide;
3-(4-Nitrobenzoxazol-2-yl)-N-(4-trifluoromethylphenyl)benzene-sulfonamide;
N-(4-Cyanophenyl)-3-(4-nitrobenzoxazol-2-yl)benzenesulfonamide;

N-(4-Chloro-3-nitrophenyl)-3-(4-nitrobenzoxazol-2-yl)benzenesulfonamide;
or
2-[3-(4-Trifluoromethylphenylsulfamoyl)phenyl]benzoxazole-7-carboxylic acid;
and the salts, solvates, hydrates and N-oxides thereof.

Compounds according to the invention are potent inhibitors of PDE7. The ability of the compounds to act in this way may be simply determined by employing a test such as those described in the Examples hereinafter.

The compounds according to the invention are of particular use in the prophylaxis and treatment of diseases in which in which inhibition of PDE7 can have a therapeutic benefit for example in autoimmune diseases such as rheumatoid arthritis, multiple sclerosis, and systemic lupus erythematosus, in transplant rejection, in graft v host disease, psoriasis, in pannus formation in rheumatoid arthritis, restenosis following angioplasty and atherosclerosis, in osteoporosis and in diseases in which cells receive pro-inflammatory signals such as asthma, inflammatory bowel disease, pancreatitis, chronic obstructive pulmonary disease, chronic bronchitis, atopic dermatitis and allergic rhinitis.

For the prophylaxis or treatment of disease the compounds according to the invention may be administered as pharmaceutical compositions, and according to a further aspect of the invention we provide a pharmaceutical composition which comprises a compound of formula (1) together with one or more pharmaceutically acceptable carriers, excipients or diluents.

Pharmaceutical compositions according to the invention may take a form suitable for oral, buccal, parenteral, nasal, topical or rectal administration, or a form suitable for administration by inhalation or insufflation.

For oral administration, the pharmaceutical compositions may take the form of, for example, tablets, lozenges or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g. pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g. lactose, microcrystalline

cellulose or calcium hydrogen phosphate); lubricants (e.g. magnesium stearate, talc or silica); disintegrants (e.g. potato starch or sodium glycollate); or wetting agents (e.g. sodium lauryl sulphate). The tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents, emulsifying agents, non-aqueous vehicles and preservatives. The preparations may also contain buffer salts, flavouring, colouring and sweetening agents as appropriate.

Preparations for oral administration may be suitably formulated to give controlled release of the active compound.

For buccal administration the compositions may take the form of tablets or lozenges formulated in conventional manner.

The compounds for formula (1) may be formulated for parenteral administration by injection e.g. by bolus injection or infusion. Formulations for injection may be presented in unit dosage form, e.g. in glass ampoule or multi dose containers, e.g. glass vials. The compositions for injection may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising, preserving and/or dispersing agents. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile pyrogen-free water, before use.

In addition to the formulations described above, the compounds of formula (1) may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation or by intramuscular injection.

For nasal administration or administration by inhalation, the compounds for use according to the present invention are conveniently delivered in the form of an aerosol spray presentation for pressurised packs or a nebuliser,

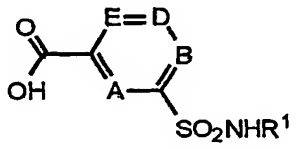
with the use of suitable propellant, e.g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas or mixture of gases.

The compositions may, if desired, be presented in a pack or dispenser device which may contain one or more unit dosage forms containing the active ingredient. The pack or dispensing device may be accompanied by instructions for administration.

The quantity of a compound of the invention required for the prophylaxis or treatment of a particular condition will vary depending on the compound chosen, and the condition of the patient to be treated. In general, however, daily dosages may range from around 100ng/kg to 100mg/kg e.g. around 0.01mg/kg to 40mg/kg body weight for oral or buccal administration, from around 10ng/kg to 50mg/kg body weight for parenteral administration and around 0.05mg to around 1000mg e.g. around 0.5mg to around 1000mg for nasal administration or administration by inhalation or insufflation.

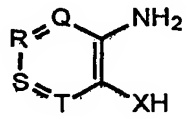
The compounds of the invention may be prepared by a number of processes as generally described below and more specifically in the Examples hereinafter. In the following process description, the symbols Q, R, S, T, X, A,B, D, E, R^1, L^1, L^2, Alk^1, r, s and R^5 when used in the text and formulae are to be understood to represent those groups described above in relation to formula (1) unless otherwise indicated. In the reactions described below, it may be necessary to protect reactive functional groups, for example hydroxy, amino, thio or carboxy groups, where these are desired in the final product, to avoid their unwanted participation in the reactions. Conventional protecting groups may be used in accordance with standard practice [see, for example, Green, T. W. in "Protective Groups in Organic Synthesis", John Wiley and Sons, 1991]. In some instances, deprotection may be the final step in the synthesis of a compound of formula (1) and the processes according to the invention described hereinafter are to be understood to extend to such removal of protecting groups.

Thus according to a further aspect of the invention, a compound of formula (1) may be prepared by coupling an acid of formula (2):



(2)

or an active derivative thereof with an amine of formula (3):



(3)

followed by cyclisation at an elevated temperature, e.g. the reflux temperature of an appropriate solvent, in the presence of a reagent such as phosphorous oxychloride or polyphosphoric acid or a derivative thereof e.g. a polyphosphate such as trimethylsilyl polyphosphate, or directly by reaction of an acid of formula (2) and an amine of formula (3) using the latter conditions

Active derivatives of acids of formula (2) include anhydrides, esters and acid halides, e.g. acid chorides, and may be obtained by standard procedures, for example as described in the Examples hereinafter.

The coupling reaction may be performed using standard conditions for reactions of this type. Thus for example the reaction may be carried out with an active derivative of the acid of formula (2) in the presence of a base, e.g. an organic base such as an amine, e.g. triethylamine or N,N-diisopropylethylamine, or a cyclic amine, such as pyridine or N-methylmorpholine, or a hydride, such as sodium hydride in an inert organic solvent such as an amide, e.g. a substituted amide such as dimethylformamide, an ether, e.g. a cyclic ether such as tetrahydrofuran or a halogenated hydrocarbon, such as dichloromethane or dichlorobenzene, at a low temperature, e.g. around -30°C to around ambient temperature.

Where an acid of formula (2) is used, the reaction may additionally be performed in the presence of a condensing agent, for example a diimide such as 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide or N,N'-dicyclohexylcarbodiimide, advantageously in the presence of a catalyst such as a N-hydroxy compound e.g. a N-hydroxytriazole such as 1-hydroxybenzotriazole. Alternatively, the acid may be reacted with a chloroformate, for example ethylchloroformate, prior to reaction with the amine of formula (3).

The acids of formula (2) may be obtained from simpler, known compounds by one or more standard synthetic methods employing substitution, oxidation, reduction or cleavage reactions as described below and in the Examples hereinafter. Particular substitution approaches include conventional alkylation, arylation, heteroarylation, acylation, thioacylation, halogenation, sulphonylation, nitration, formylation and coupling procedures. It will be appreciated that these methods may also be used to obtain or modify other compounds of formula (1) where appropriate functional groups exist in these compounds. Additionally, although a number of the intermediate amines of formula (3) for use in the coupling reaction described above are known, others can be derived therefrom using these standard synthetic methods.

Thus compounds of the invention and intermediates thereto may be prepared by alkylation, arylation or heteroarylation. For example, compounds containing a $-L^1H$, $-L^1(Alk^1)_rL^2H$ or $-Alk^1L^2H$, group (where L^1 and L^2 is each a linker atom or group) may be treated with an alkylating agent $(R^5)_sL^2Alk^1X^1$ or $(R^5)_sX^1$ in which X^1 is a leaving atom or group such as a halogen atom, e.g. a fluorine, bromine, iodine or chlorine atom or a sulphonyloxy group such as an alkylsulphonyloxy, e.g. trifluoromethylsulphonyloxy or arylsulphonyloxy, e.g. p-toluenesulphonyloxy group.

The reaction may be carried out in the presence of a base such as a carbonate, e.g. caesium or potassium carbonate, an alkoxide, e.g. potassium t-butoxide, or a hydride, e.g. sodium hydride, in a dipolar aprotic solvent such as an amide, e.g. a substituted amide such as

dimethylformamide or an ether, e.g. a cyclic ether such as tetrahydrofuran.

In another example, compounds containing a $-L^1H$, $-L^1(Alk^1)_rL^2H$ or $-Alk^1L^2H$ group as defined above may be functionalised by acylation or thioacylation, for example by reaction with one of the alkylating agents just described but in which X^1 is replaced by a $-C(O)X^2$, $C(S)X^2$, $-N(R^6)COX^2$ or $-N(R^6)C(S)X^2$ group in which X^2 is a leaving atom or group as described for X^1. The reaction may be performed in the presence of a base, such as a hydride, e.g. sodium hydride or an amine, e.g. triethylamine or N-methyl-morpholine, in a solvent such as a halogenated hydrocarbon, e.g. dichloromethane or carbon tetrachloride or an amide, e.g. dimethylformamide, at for example ambient temperature. Alternatively, the acylation or thioacylation may be carried out under the same conditions with an acid or thioacid (for example one of the alkylating agents described above in which X^1 is replaced by a $-CO_2H$ or -COSH group) in the presence of a condensing agent, for example a diimide such as 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide or N,N'-dicyclohexylcarbodiimide, advantageously in the presence of a catalyst such as a N-hydroxy compound e.g. a N-hydroxytriazole such as 1-hydroxybenzotriazole. Alternatively the acid may be reacted with a chloroformate, for example ethylchloroformate, prior to the desired acylation reaction.

In a further example compounds may be obtained by sulphonylation of a compound containing an -OH group by reaction with one of the above alkylating agents but in which X^1 is replaced by a $-S(O)Hal$ or $-SO_2Hal$ group in which Hal is a halogen atom such as chlorine atom in the presence of a base, for example an inorganic base such as sodium hydride in a solvent such as an amide, e.g. a substituted amide such as dimethylformamide at for example ambient temperature.

In another example, compounds containing a $-L^1H$, $-L^2H$ or $-L^3H$ group as defined above may be coupled with one of the alkylation agents just described but in which X^1 is replaced by an -OH group in a solvent such as tetrahydrofuran in the presence of a phosphine, e.g. triphenylphosphine and an activator such as diethyl, diisopropyl- or dimethylazodicarboxylate.

In a further example, ester groups $-CO_2R^6$ in the compounds may be converted to the corresponding acid [$-CO_2H$] by acid- or base-catalysed hydrolysis depending on the nature of the group R^6. Acid- or base-catalysed hydrolysis may be achieved for example by treatment with an organic or inorganic acid, e.g. trifluoroacetic acid in an aqueous solvent or a mineral acid such as hydrochloric acid in a solvent such as dioxan or an alkali metal hydroxide, e.g. lithium hydroxide in an aqueous ether or alcohol, e.g. an aqueous cyclic ether such as aqueous tetrahydrofuran or an aqueous alcohol such as aqueous methanol at ambient or at an elevated temperature.

In a further example, $-OR^6$ groups [where R^6 represents an alkyl group such as methyl group] in compounds of formula (1) may be cleaved to the corresponding alcohol -OH by reaction with for example boron tribromide in a solvent such as a halogenated hydrocarbon, e.g. dichloromethane at a low temperature, e.g. around -78°C.

Alcohol [-OH] groups may also be obtained by hydrogenation of a corresponding $-OCH_2R^5$ group (where R^5 is an aryl group) using a metal catalyst, for example palladium on a support such as carbon in a solvent such as ethanol in the presence of ammonium formate, cyclohexadiene or hydrogen, from around ambient to the reflux temperature. In another example, -OH groups may be generated from the corresponding ester [$-CO_2R^6$] or aldehyde [-CHO] by reduction, using for example a complex metal hydride such as lithium aluminium hydride or sodium borohydride in a solvent such as methanol.

In another example, alcohol -OH groups in the compounds may be converted to a corresponding $-OR^6$ group (where R^6 is an optionally substituted alkyl group) by coupling with a reagent R^6OH in a solvent such as tetrahydrofuran in the presence of a phosphine, e.g. triphenylphosphine and an activator such as diethyl-, diisopropyl-, or dimethylazodicarboxylate.

Aminosulphonylamino [$-NHSO_2NH_2$] groups in the compounds may be obtained, in another example, by reaction of a corresponding amine [$-NH_2$]

with sulphamide in the presence of an organic base such as pyridine at an elevated temperature, e.g. the reflux temperature of an appropriate solvent.

In a further example amine ($-NH_2$) groups may be alkylated using a reductive alkylation process employing an aldehyde and a borohydride, for example sodium triacetoxyborohydride or sodium cyanoborohydride, in a solvent such as a halogenated hydrocarbon, e.g. dichloromethane, a ketone such as acetone, or an alcohol, e.g. ethanol, where necessary in the presence of an acid such as acetic acid at around ambient temperature.

In a further example, amine [$-NH_2$] groups in the compounds may be obtained by hydrolysis from a corresponding imide by reaction with hydrazine in a solvent such as an alcohol, e.g. ethanol at ambient temperature.

In another example, a nitro [$-NO_2$] group may be reduced to an amine [$-NH_2$], for example by catalytic hydrogenation using for example hydrogen in the presence of a metal catalyst, for example palladium on a support such as carbon in a solvent such as an ether, e.g. tetrahydrofuran or an alcohol e.g. methanol, or by chemical reduction using for example a metal, e.g. tin or iron, in the presence of an acid such as hydrochloric acid. Catalytic hydrogenation is particularly useful for the preparation of intermediate amines of formula (3) from their corresponding nitro analogues.

Aromatic halogen substituents in the compounds may be subjected to halogen-metal exchange with a base, for example a lithium base such as n-butyl or t-butyl lithium, optionally at a low temperature, e.g. around -78°C, in a solvent such as tetrahydrofuran and then quenched with an electrophile to introduce a desired substituent. Thus, for example, a formyl group may be introduced by using dimethylformamide as the electrophile; a thiomethyl group may be introduced by using dimethyldisulphide as the electrophile.

In another example, sulphur atoms in the compounds, for example when present in a linker group L^1, L^2 or L^3 may be oxidised to the corresponding sulphoxide or sulphone using an oxidising agent such as a peroxy acid, e.g. 3-chloroperoxybenzoic acid, in an inert solvent such as a halogenated hydrocarbon, e.g. dichloromethane, at around ambient temperature.

N-oxides of compounds of formula (1) may be prepared for example by oxidation of the corresponding nitrogen base using an oxidising agent such as hydrogen peroxide in the presence of an acid such as acetic acid, at an elevated temperature, for example around 70°C to 80°C, or alternatively by reaction with a peracid such as peracetic acid in a solvent, e.g. dichloromethane, at ambient temperature.

Salts of compounds of formula (1) may be prepared by reaction of a compound of formula (1) with an appropriate base in a suitable solvent or mixture of solvents e.g. an organic solvent such as an ether e.g. diethylether, or an alcohol, e.g. ethanol using conventional procedures.

Where it is desired to obtain a particular enantiomer of a compound of formula (1) this may be produced from a corresponding mixture of enantiomers using any suitable conventional procedure for resolving enantiomers.

Thus for example diastereomeric derivatives, e.g. salts, may be produced by reaction of a mixture of enantiomers of formula (1) e.g. a racemate, and an appropriate chiral compound, e.g. a chiral base. The diastereomers may then be separated by any convenient means, for example by crystallisation and the desired enantiomer recovered, e.g. by treatment with an acid in the instance where the diastereomer is a salt.

In another resolution process a racemate of formula (1) may be separated using chiral High Performance Liquid Chromatography. Alternatively, if desired a particular enantiomer may be obtained by using an appropriate chiral intermediate in one of the processes described above.

Chromatography, recrystallization and other conventional separation procedures may also be used with intermediates or final products where it is desired to obtain a particular geometric isomer of the invention.

The following Examples illustrate the invention.

All temperatures are in °C.

INTERMEDIATE 1

3-(4-Chlorophenylsulfamoyl)benzoic acid

A mixture of 3-(chlorosulfonyl)benzoic acid (500mg), 4-chloroaniline (304mg) and pyridine (0.92ml) in dichloromethane (30ml) was stirred overnight at room temperature under an atmosphere of nitrogen. The mixture was diluted with 10% methanol in dichloromethane (30ml) and then washed with 2N hydrochloric acid (100ml) and water (80ml). The organic phase was dried (magnesium sulfate) and the solvent removed *in vacuo* to give a pink solid. Purification by column chromatography on silica eluting with 50% ethyl acetate in hexane and then ethyl acetate gave the title compound (257mg) as a white solid.

TLC R_f 0.4 (50% ethyl acetate in hexane).

The following compounds were prepared by a similar procedure:

INTERMEDIATE 2

3-(4-Chloro-2-methylphenylsulfamoyl)benzoic acid

Prepared from 3-(chlorosulfonyl)benzoic acid (3.09g) and 4-chloro-2-methylaniline (2.38g) to give the title compound (3.07g) as a pale pink solid.

TLC R_f 0.34 (50% ethyl acetate in hexane).

INTERMEDIATE 3

3-(2-Chlorophenylsulfamoyl)benzoic acid

Prepared from 3-(chlorosulfonyl)benzoic acid (500mg) and 2-chloroaniline (0.24ml) to yield the title compound (291mg).

TLC R_f 0.52 (50% ethyl acetate in hexane).

INTERMEDIATE 4

3-(3-Cyanophenylsulfamoyl)benzoic acid

Prepared from 3-(chlorosulfonyl)benzoic acid (800mg) and 3-aminobenzonitrile (510mg) to yield the title compound (590mg).

TLC R_f 0.43 (50% ethyl acetate in hexane).

INTERMEDIATE 5

3-(3,5-Dichlorophenylsulfamoyl)benzoic acid

Prepared from 3-(chlorosulfonyl)benzoic acid (800mg) and 3,5-dichloroaniline (587mg) to provide the title compound (550mg) as a white solid.

TLC R_f 0.4 (50% ethyl acetate in hexane).

INTERMEDIATE 6

3-(4-Bromo-2-chlorophenylsulfamoyl)benzoic acid

Prepared from 3-(chlorosulfonyl)benzoic acid (600mg) and 4-bromo-2-chloroaniline (562mg) to provide the title compound (250mg) as a white solid.

TLC R_f 0.54 (50% ethyl acetate in hexane).

INTERMEDIATE 7

3-(4-Ethylcarbamoyl-phenylsulfamoyl)benzoic acid

Prepared from 3-(chlorosulfonyl)benzoic acid (600mg) and N-ethyl-4-aminobenzamide (447mg) to furnish the title compound (550mg) as an off-white solid.

TLC R_f 0.48 (ethyl acetate).

INTERMEDIATE 8

3-(4-Bromophenylsulfamoyl)benzoic acid

Prepared from 3-(chlorosulfonyl)benzoic acid (0.5g) and 4-bromoaniline (0.39g) to give the title compound (0.65g) as an off white solid.

TLC R_f 0.4 (50% hexane in ethyl acetate).

INTERMEDIATE 9

3-(2-Methoxycarbonylphenylsulfamoyl)benzoic acid

Prepared from 3-(chlorosulfonyl)benzoic acid (2.0g) and methyl anthranilate (1.2ml), to give the title compound (1.4g) as an off white solid.

TLC R_f 0.7 (ethyl acetate).

INTERMEDIATE 10

3-(4-Trifluoromethyl-phenylsulfamoyl)benzoic acid

Prepared from 3-(chlorosulfonyl)benzoic acid (0.6g) and 4-aminobenzotrifluoride (0.36ml), to give the title compound (0.7g) as a pale orange solid.

TLC R_f 0.42 (50% hexane in ethyl acetate).

INTERMEDIATE 11

3-(4-Cyanophenylsulfamoyl)benzoic acid

Prepared from 3-(chlorosulfonyl)benzoic acid (0.5g) and 4-aminobenzonitrile (0.268g), to give the title compound (0.205g)as an off white solid.

TLC R_f 0.36 (50% hexane in ethyl acetate).

INTERMEDIATE 12

3-(4-Chloro-3-nitrophenylsulfamoyl)benzoic acid

Prepared from 3-(chlorosulfonyl)benzoic acid (0.5g) and 4-chloro-3-nitroaniline (0.39g), to give the title compound (0.35g) as an off white solid.

TLC R_f 0.40 (50% hexane in ethyl acetate).

INTERMEDIATE 13

4-(3-Hydroxycarbonylbenzenesulfonylamino)benzoic acid ethyl ester

A mixture of 3-(chlorosulfonyl)benzoic acid (3.0g), ethyl 4-aminobenzoate (2.36g) and pyridine (1.06ml) in dichloromethane (30ml) was stirred overnight at room temperature under an atmosphere of nitrogen. The mixture was diluted with dichloromethane (100ml) and washed with 1N hydrochloric acid (100ml). Ethyl acetate (100ml) was added to the dichloromethane, the combined organics were washed with brine (100ml)

and the solvent was removed *in vacuo*. The residue was triturated with dichloromethane to give the title compound (2.95g) as a pink solid.
TLC R_f 0.17 (40% ethyl acetate in hexane).

INTERMEDIATE 14
4-(3-Chlorocarbonylbenzenesulfonylamino)benzoic acid ethyl ester
Oxalyl chloride (1.1ml) and N,N-dimethylformamide (10 drops) were added to a mixture of 4ñ(3-hydroxycarbonylbenzenesulfonylamino)benzoic acid ethyl ester (2.95g) in dichloromethane (40ml) under an atmosphere of nitrogen and the reaction was stirred at room temperature for 2h. The solvent was removed *in vacuo* to give the title compound (3.11g) as a cream solid.
TLC R_f 0.57 (40% ethyl acetate in hexane).

INTERMEDIATE 15
2,3-Dinitrobenzoic acid methyl ester
A solution of 2,3-dinitrobenzoic acid (500mg) in methanol (30ml) was cooled to 0(C under a nitrogen atmosphere. Acetyl chloride (1.78ml) was added over a period of 10 minutes and the reaction was stirred for 10 minutes at 0º then at room temperature for 60h. Further acetyl chloride (0.89ml) was then added and the reaction heated to 50º for 18h. The solvent was removed *in vacuo* and the residue partitioned between 5% methanol in dichloromethane (30ml) and 2N sodium hydroxide solution (50ml). The organic phase was dried (magnesium sulfate) and the solvent removed *in vacuo* to give the title compound (290mg) as a yellow solid.
TLC R_f 0.82 (dichloromethane).

INTERMEDIATE 16
2,3-Diaminobenzoic acid methyl ester
A mixture of 2,3-dinitrobenzoic acid methyl ester (290mg) in ethanol (30ml) was hydrogenated under atmospheric conditions in the presence of 10% palladium on carbon (catalytic). The mixture was then filtered through Celite™ and washed through with ethanol (50ml). The solvent was removed *in vacuo* to give the title compound (217mg) as a brown solid.
TLC R_f 0.5 (dichloromethane).

INTERMEDIATE 17

N-Ethyl-4-nitrobenzamide

A mixture of 4-nitrobenzoyl chloride (2.0g), ethylamine (2.0M solution in tetrahydrofuran, 13.5ml) and potassium carbonate (8.0g) in tetrahydrofuran (40ml) was stirred under nitrogen at room temperature for 18h. The solvent was removed *in vacuo* and the residue was partitioned between dichloromethane (100ml) and water (80ml). The aqueous phase was extracted with further dichloromethane (50ml) and the combined organic phases were dried (magnesium sulfate). The solvent was removed *in vacuo* to furnish the title compound (1.88g) as a pale yellow solid.

TLC R_f 0.4 (50% ethyl acetate in hexane).

INTERMEDIATE 18

N-Ethyl-4-aminobenzamide

A solution of N-ethyl-4-nitrobenzamide (1.88g) in ethanol (100ml) was hydrogenated at atmospheric pressure in the presence of a catalytic amount of 10% palladium on carbon for 3.5h. The reaction mixture was filtered through Celite™ and washed through with ethanol (50ml). The solvent was then removed *in vacuo* and the residue dried under high vacuum to afford the title compound (1.56g) as a pale pink solid.

TLC R_f 0.48 (ethyl acetate).

INTERMEDIATE 19

2-Hydroxyanthranilic acid methyl ester

A suspension of 2-hydroxyanthranilic acid (0.5g) in methanol (20ml) was treated with concentrated hydrochloric acid (1ml) and the mixture heated to reflux for 24h. The mixture was cooled, diluted with water (20ml) and basified to pH 10 with saturated aqueous sodium hydrogen carbonate solution. The product was extracted with dichloromethane (3 x 50 ml), the extracts were combined, dried (magnesium sulfate) and the filtrate evaporated *in vacuo* to give the title compound (0.28g) as a brown solid.

TLC R_f 0.7 (50% ethyl acetate in hexane).

The following compound was prepared by a similar procedure:

INTERMEDIATE 20

3-Amino-2-hydroxybenzoic acid methyl ester

Prepared from 3-aminosalicylic acid (0.5g) to give the title compound (0.04g) as a tan solid.

TLC R_f 0.8 (ethyl acetate).

EXAMPLE 1

N-(4-Chlorophenyl)-3-(7-nitro-1H-benzimidazol-2-yl)benzene-sulfonamide

A mixture of 3-(4-chlorophenylsulfamoyl)benzoic acid (120mg), 3-nitro-1,2-phenylenediamine (59mg) and trimethylsilyl polyphosphate (1ml) in 1,2-dichlorobenzene (10ml) was heated to reflux for 2h under a nitrogen atmosphere and then left to stand at room temperature for 36h. The mixture was diluted with water (30ml), neutralized with 2N sodium hydroxide and extracted with dichloromethane (4 x 30ml). The combined organic phases were dried (magnesium sulfate) and the solvent was removed *in vacuo*. The residue was purified by column chromatography on silica eluting with 50% ethyl acetate in hexane to give the title compound (19mg) as a yellow solid.

TLC R_f 0.43 (50% ethyl acetate in hexane).

^{1}H NMR (200MHz, DMSO-d^6) 7.10 (2H, d), 7.30 (2H, d), 7.50 (1H, t), 7.70-7.80 (1H, m), 7.85-7.95 (1H, m), 8.10-8.20 (2H, m), 8.55-8.65 (1H, m), 8.80 (1H, s).

The following compounds were prepared by a similar procedure:

EXAMPLE 2

N-(4-Cyanophenyl)-3-(7-nitro-1H-benzimidazol-2-yl)benzene-sulfonamide

Prepared from 3-nitro-1,2-phenylenediamine (51mg) and 3-(4-cyano-phenylsulfamoyl)benzoic acid (100mg) to provide the title compound (17mg) as an orange solid.

TLC R_f 0.33 (5% methanol in dichloromethane).

^{1}H NMR (200MHz, DMSO-d^6) 7.30 (2H, d), 7.49 (1H, t), 7.69 (2H, d), 7.55-782 (1H, m), 7.97 (1H, d), 8.15-8.26 (2H, m), 8.67 (1H, d), 8.90 (1H, s).

EXAMPLE 3

N-(2-Chlorophenyl)-3-(7-nitro-1H-benzimidazol-2-yl)-benzene-sulfonamide

Prepared from 3-nitro-1,2-phenylenediamine (62mg) and 3-(2-chloro-phenylsulfamoyl)benzoic acid (127mg) to provide the title compound (15mg) as a yellow solid.

TLC R_f 0.55 (50% ethyl acetate in hexane).

^{1}H NMR (200MHz, DMSO-d^6) 7.15-7.30 (3H, m), 7.39-7.50 (2H, m), 7.72-7.39 (2H, m), 8.14-8.25 (2H, m), 8.69 (1H, d), 8.79 (1H, s).

EXAMPLE 4

N-(3-Cyanophenyl)-3-(7-nitro-1H-benzimidazol-2-yl)benzene-sulfonamide

Prepared from 3-nitro-1,2-phenylenediamine (101mg) and 3-(3-cyano-phenylsulfamoyl)benzoic acid (200mg) to provide the title compound (64mg) as an orange solid.

TLC R_f 0.48 (5% methanol in dichloromethane).

^{1}H NMR (200MHz, DMSO-d^6) 7.42-7.54 (5H, m), 7.78 (1H, t), 7.94 (1H, d), 8.15-8.28 (2H, m), 8.67 (1H, d), 8.87 (1H, s), 10.98 (1H, s), 13.56 (1H, s).

EXAMPLE 5

N-(3,5-Dichlorophenyl)-3-(7-nitro-1H-benzimidazol-2-yl)benzene-sulfonamide

Prepared from 3-nitro-1,2-phenylenediamine (88mg) and 3-(3,5-dichloro-phenylsulfamoyl)benzoic acid (200mg) to provide the title compound (82mg) as a pale orange solid.

TLC R_f 0.4 (50% ethyl acetate in hexane).

^{1}H NMR (200MHz, $CDCl_3$) 7.07 (1H, s), 7.09 (1H, s), 7.10 (1H, s), 7.38 (1H, t), 7.68 (1H, t), 7.96 (1H, d), 8.05-8.20 (4H, m), 8.45 (1H, d), 8.81 (1H, s).

EXAMPLE 6

N-(4-Bromo-2-chlorophenyl)-3-(7-nitro-1H-benzimidazol-2-yl)-benzenesulfonamide

Prepared from 3-nitro-1,2-phenylenediamine (98mg) and 3-(4-bromo-2-chlorophenylsulfamoyl)benzoic acid (250mg) to provide the title compound (43mg) as a brown solid.

TLC R_f 0.45 (50% ethyl acetate in hexane).

^{1}H NMR (200MHz, $CDCl_3$) 7.11 (1H, s), 7.42-7.51 (3H, m), 7.65 (1H, d), 7.73 (1H, d), 7.90 (1H, d), 8.21 (1H, d), 8.26 (1H, d), 8.41 (1H, d), 8.59 (1H, s).

EXAMPLE 7

N-Ethyl-4-[3-(7-nitro-1H-benzimidazol-2-yl)benzenesulfonylamino]-benzamide

Prepared from 3-nitro-1,2-phenylenediamine (88mg) and 3-(4-ethyl-carbamoylphenylsulfamoyl)benzoic acid (200mg) to provide the title compound (14mg) as a yellow solid.

TLC R_f 0.5 (ethyl acetate).

^{1}H NMR (400MHz, $CDCl_3$) 1.11 (3H, t), 3.29 (2H, q), 7.26-7.33 (2H, m), 7.41 (1H, t), 7.65-7.70 (2H, m), 7.90-7.95 (2H, m), 8.05-8.13 (3H, m), 8.23 (2H, d), 8.35 (1H, s), 8.75 (1H, t), 10.86 (1H, s), 13.07 (1H, s).

EXAMPLE 8

4-[3-(7-Nitro-1H-benzimidazol-2-yl)benzenesulfonylamino]benzoic acid ethyl ester

3-Nitro-1,2-phenylenediamine (319mg) and pyridine (0.34ml) were added to a suspension of 4-(3-chlorocarbonylbenzenesulfonylamino)benzoic acid ethyl ester (765mg) in dichloromethane (40ml) under a nitrogen atmosphere. The reaction was stirred at room temperature for 5h and then left to stand for 2 days. The mixture was diluted with dichloromethane (30ml) and washed with saturated aqueous sodium bicarbonate solution (80ml). The organic phase was dried (magnesium sulfate) and the solvent removed *in vacuo* to give the amide as a mixture of isomers. The crude amide was combined with phosphorus oxychloride (10ml) under a nitrogen atmosphere, heated to reflux for 100 minutes, then allowed to cool. The mixture was poured into ice-water (100ml) and neutralized with 2N sodium hydroxide solution. Saturated aqueous sodium bicarbonate solution (60ml) was added and the aqueous phase was extracted with ethyl acetate (3 x 70ml). Water (150ml) was added to

the combined organic phases and the pH was adjusted to 3 with 2N aqueous hydrochloric acid. The organic layer was washed with brine (100ml), dried (magnesium sulfate) and the solvent removed *in vacuo* to give a brown solid. Purification by column chromatography on silica eluting with 33% hexane in ethyl acetate gave the title compound (80mg) as a brown solid.

TLC R_f 0.64 (33% hexane in ethyl acetate).

^{1}H NMR (400MHz, 130°, DMSO-d^6) 1.25 (3H, t), 4..25 (2H, q), 7.30 (2H, d), 7.40-7.45 (1H, t), 7.70-7.75 (1H, t), 7.80 (2H, d), 7.95-8.00 (1H, m), 8.15 (2H, bs), 8.45-8.55 (1H, m), 8.80 (1H, s).

EXAMPLE 9

2-[3-(4-Chloro-2-methylphenylsulfamoyl)phenyl]-3H-benzimidazole-5-carboxylic acid methyl ester

1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (441mg) and methyl 3,4-diaminobenzoate (255mg) were added to a suspension of 3-(4-chloro-2-methyl-phenylsulfamoyl)benzoic acid (500mg) in dichloromethane (40ml) under a nitrogen atmosphere. The reaction was stirred at room temperature for 18h. The mixture was diluted with dichloromethane (20ml) then washed with water (100ml) and saturated aqueous sodium bicarbonate solution (100ml). The organic phase was dried (magnesium sulfate) and the solvent was removed *in vacuo* to give the amide as a mixture of isomers. The crude amide was combined with phosphorus oxychloride (10ml) under a nitrogen atmosphere, heated to reflux for 1h and then allowed to cool. The mixture was poured into ice-water (100ml) and neutralized with 2N aqueous sodium hydroxide solution. Saturated aqueous sodium bicarbonate solution (60ml) was added and the aqueous phase was extracted with ethyl acetate (3 x 70ml). The combined organic phases were dried (magnesium sulfate) and the solvent was removed *in vacuo* to give the title compound (700mg) as a pale brown solid.

TLC R_f 0.6 (33% hexane in ethyl acetate).

^{1}H NMR (200MHz, DMSO-d^6) 2.00 (3H, s), 3.90 (3H, s), 6.95 (1H, d), 7.10-7.25 (2H, m), 7.60-7.90 (4H, m), 8.15-8.35 (1H, m), 8.40-8.50 (1H, m), 8.60 (1H, s), 9.85-9.95 (1H, bs), 13.60 (1H, s).

The following compounds were prepared by a similar procedure:

EXAMPLE 10

N-(4-Chloro-2-methylphenyl)-3-(7-nitro-1H-benzimidazol-2-yl)-benzenesulfonamide

Prepared from 3-(4-chloro-2-methylphenylsulfamoyl)benzoic acid (300mg) and 3-nitro-1,2-phenylenediamine (141mg) to give the title compound (187mg) as a pale brown solid.

TLC R_f 0.4 (5% methanol in dichloromethane).

^1H NMR (200MHz, DMSO-d^6) 2.05 (3H, s), 6.95 (1H, d), 7.15-7.25 (1H, m), 7.30 (1H, s), 7.45-7.55 (1H, m), 7.75-7.85 (2H, m), 8.10-8.25 (2H, m), 8.60-8.80 (2H, b).

EXAMPLE 11

2-[3-(2-Chlorophenylsulfamoyl)phenyl]-3H-benzimidazole-4-carboxylic acid methyl ester

Prepared from 2,3-diaminobenzoic acid methyl ester (67mg) and 3-(2-chlorophenylsulfamoyl)benzoic acid (126mg) to afford the title compound (54mg) as an off-white solid.

TLC R_f 0.4 (50% ethyl acetate in hexane).

^1H NMR (200MHz, $CDCl_3$) 4.07 (3H, s), 7.06-7.14 (2H, m), 7.26-7.42 (3H, m), 7.65 (1H, t), 7.76 (1H, d), 7.88 (1H, d), 7.79 (1H, d), 8.07 (1H, d), 8.39 (1H, d), 8.46 (1H, s).

EXAMPLE 12

2-[3-(4-Chloro-2-methylphenylsulfamoyl)phenyl]-1H-benzimidazole-4-carboxylic acid methyl ester

Prepared from 3-(4-chloro-2-methylphenylsulfamoyl)benzoic acid (425mg) and 2,3-diaminobenzoic acid methyl ester (217mg) to give the title compound (540mg) as a brown solid.

TLC R_f 0.52 (5% methanol in dichloromethane).

^1H NMR (200MHz, DMSO-d^6) 2.00 (3H, s), 4.00 (3H, s), 6.95 (1H, d), 7.10-7.20 (1H, m), 7.25 (1H, s), 7.30-7.45 (1H, m), 7.75 (2H, d), 7.85 (1H, d), 8.05 (1H, d), 8.55-8.65 (1H, m), 8.70 (1H, s), 9.90 (1H, s), 12.75 (1H, s).

EXAMPLE 13

2-[3-(5-Chloro-1H-benzimidazol-2-yl)benzenesulfonylamino]benzoic acid methyl ester

Prepared from 3-(2-ethoxycarbonyl-phenylsulfamoyl)benzoic acid (500mg) and 4-chloro-1,2-phenylenediamine (180mg) to yield the title compound (172mg) as a white solid.

TLC R_f 0.84 (ethyl acetate).

^{1}H NMR (200MHz, DMSO-d^6) 3.79 (3H, s), 7.18 (1H, dt), 7.27 (1H, dd), 7.45-7.91 (7H, m), 8.40 (1H, d), 8.63 (1H, s), 10.55 (1H, s).

EXAMPLE 14

2-[3-(4-Chloro-2-methylphenylsulfamoyl)phenyl]-3H-benzimidazole-5-carboxylic acid

A mixture of 2-[3-(4-chloro-2-methylphenylsulfamoyl)phenyl]-3H-benzimidazole-5-carboxylic acid methyl ester (200mg) and lithium hydroxide monohydrate (128mg) in tetrahydrofuran (8ml) and water (8ml) was stirred at room temperature for 2 days, then heated at 50° for 5h and allowed to cool overnight. The tetrahydrofuran was removed *in vacuo* and the aqueous phase was diluted with 2N aqueous sodium hydroxide solution (10ml) then washed with ethyl acetate (30ml). The aqueous phase was acidified to pH 5 with 2N aqueous hydrochloric acid and the resulting precipitate was extracted with ethyl acetate (2 x 25ml). The combined organic phases were washed with brine (50ml), dried (magnesium sulfate) and the solvent was removed *in vacuo*. The residue was triturated with diethyl ether to give a pale brown solid. Purification by preparative HPLC (Phenomenex Luna C-18 (250 x 21.2mm column) eluting with 0.05% trifluoroacetic acid in water and 0.05% trifluoroacetic acid in acetonitrile) gave the title compound (66mg) as a white solid.

TLC R_f 0.63 (ethyl acetate).

^{1}H NMR (200MHz, DMSO-d^6) 2.05 (3H, s), 6.95 (2H, d), 7.15-7.25 (1H, m), 7.30 (1H, s), 7.70-7.95 (4H, m), 8.20 (1H, s), 7.90-7.95 (1H, m), 8.60 (1H, s), 9.90 (1H, s).

The following compound was prepared by a similar procedure:

EXAMPLE 15

2-[3-(4-Chloro-2-methylphenylsulfamoyl)phenyl]-3H-benzimidazole-4-carboxylic acid

Prepared from 2-[3-(4-chloro-2-methyl-phenylsulfamoyl)phenyl]-1H-benzimidazole-4-carboxylic acid methyl ester (158mg) to give the title compound (121mg) as a brown solid.

TLC R_f 0.21 (5% methanol in dichloromethane).

^{1}H NMR (200MHz, DMSO-d^6) 2.05 (3H, s), 6.95 (1H, d), 7.15-7.25 (1H, m), 7.30 (1H, s), 7.30-7.45 (1H, m), 7.70-8.05 (4H, m), 8.60-8.75 (2H, m), 9.85 (1H, s), 12.75 (1H, s), 13.20-13.40 (1H, b).

EXAMPLE 16

2-[3-(5-Chloro-1H-benzimidazol-2-yl)benzenesulfonylamino]benzoic acid

A solution of 2-[3-(5-chloro-1H-benzimidazol-2-yl)benzenesulfonylamino]-benzoic acid methyl ester (60mg) and lithium hydroxide monohydrate (30mg) in tetrahydrofuran (2ml) and water (1ml) was stirred for 2.5h at 50°, then allowed to cool. The mixture was acidified with 2N aqueous hydrochloric acid, diluted with water and extracted with ethyl acetate (20ml). The organic extract was dried (magnesium sulfate) and concentrated *in vacuo* to afford the title compound (53mg) as a white solid.

TLC R_f 0.15 (50% ethyl acetate in hexane).

^{1}H NMR (200MHz, DMSO-d^6) 7.10-7.19 (1H, m), 7.28 (1H, dd), 7.55-7.95 (7H, m), 8.40 (1H, d), 8.69 (1H, s), 11.24 (1H, s).

The following compound was prepared by a similar procedure:

EXAMPLE 17

2-[3-(2-Chlorophenylsulfamoyl)phenyl]-3H-benzimidazole-4-carboxylic acid

Prepared from 2-[3-(2-chlorophenylsulfamoyl)phenyl]-3H-benzimidazole-4-carboxylic acid methyl ester (47mg) to afford the title compound (47mg) as a white solid.

TLC Rf 0.15 (50% ethyl acetate in hexane).

^{1}H NMR (200MHz, $CDCl_3$) 7.15-7.42 (5H, m), 7.68-7.87 (3H, m), 7.95 (1H, d), 8.60 (1H, d), 8.71 (1H, s).

EXAMPLE 18

2-[3-(4-Chloro-2-methylphenylsulfamoyl)phenyl]benzoxazole-7-carboxylic acid

A mixture of methyl ester (68mg), in tetrahydrofuran (10ml) was treated with a solution of lithium hydroxide (14mg) in water (10ml). The mixture was stirred at room temperature overnight and then the organic solvent was removed *in vacuo*. The aqueous residue was washed with dichloromethane (20ml), acidified with 2N hydrochloric acid and extracted with dichloromethane (2 x 20ml). The organic extracts were combined, dried (magnesium sulfate) and evaporated *in vacuo* to give the title compound (40mg) as an off white solid.

TLC R_f 0.28 (50% hexane in ethyl acetate).

^{1}H NMR (200 MHz, DMSO-d^6) 2.00 (3H, s), 6.95 (1H, d), 7.20 (1H, dd), 7.25 (1H, s), 7.55 (1H, t), 7.80 (2H, d), 8.00 (1H, d), 8.15 (1H, d), 8.45 (1H, m), 8.55 (1H, s).

The following compounds were prepared by a similar procedure:

EXAMPLE 19

2-[3-(5-Chlorobenzoxazol-2-yl)benzenesulfonylamino]benzoic acid

Prepared from 2-[3-(5-chlorobenzoxazol-2-yl)benzenesulfonylamino]-benzoic acid methyl ester (0.24g) to give the title compound (0.15g) as an off white solid.

TLC R_f 0.59 (50% ethyl acetate in hexane).

^{1}H NMR (200MHz DMSO-d^6) 7.10 (1H, t), 7.50-7.60 (3H, m), 7.70-8.10 (5H, m), 8.40 (1H, d), 8.55 (1H, s).

EXAMPLE 20

2-[3-(4-Chloro-2-methylphenylsulfamoyl)phenyl]benzoxazole-4-carboxylic acid

Prepared from 2-[3-(4-chloro-2-methylphenylsulfamoyl)phenyl]benzox-azole-4-carboxylic acid methyl ester (68mg) to give the title compound (10mg) as an off-white solid.

TLC R_f 0.7 (ethyl acetate).

^{1}H NMR (200 MHz, DMSO-d^6) 2.00 (3H, s), 6.95 (1H, d), 7.15 (1H, dd), 7.25 (1H, s), 7.55 (1H, t), 7.80-7.85 (2H, m), 7.95 (1H, d), 8.10 (1H, d), 8.44-8.50 (1H, m), 8.60 (1H, s).

EXAMPLE 21

N-(4-Chloro-2-methylphenyl)-3-(4-nitrobenzoxazol-2-yl)benzene-sulfonamide

A mixture of 3-(4-chloro-2-methylphenylsulfamoyl)benzoic acid (210mg), 2-amino-3-nitrophenol (100mg) and trimethylsilyl polyphosphate (3ml) in 1,2-dichlorobenzene (10ml) was heated to reflux for 2h under a nitrogen atmosphere, then allowed to cool. The mixture was poured into water (100ml) and neutralized with 2N aqueous sodium hydroxide solution. The mixture was extracted with dichloromethane (2 x 70ml) and the combined organic phases were dried (magnesium sulfate) and the solvent was removed *in vacuo*. The residue was purified by column chromatography on silica, eluting with 10-50% ethyl acetate in hexane. The red solid obtained was partitioned between ethyl acetate (50ml) and 2N sodium hydroxide solution (50ml). The organic phase was washed with brine, dried (magnesium sulfate) and the solvent was removed *in vacuo*. Trituration with diethyl ether afforded the title compound (54mg) as a cream solid.

TLC R_f 0.70 (50% ethyl acetate in hexane).

^{1}H NMR (200MHz, DMSO-d^6) 2.05 (3H, s), 6.95 (1H, d), 7.15-7.25 (1H, m), 7.30 (1H, s), 7.65-7.75 (1H, m), 7.80-7.95 (2H, m), 8.35-8.40 (2H, m), 8.50-8.60 (1H, m), 8.65 (1H, s), 10.05 (1H, s).

EXAMPLE 22

2-[3-(5-Chlorobenzoxazol-2-yl)benzenesulfonylamino]benzoic acid methyl ester

Prepared from 3-(2-methoxycarbonylphenylsulfamoyl)benzoic acid (0.5g) and 2-amino-3-chlorophenol (0.18g) to give the title compound (0.24g) as an off-white solid.

TLC R_f 0.63 (50% hexane in ethyl acetate).

^{1}H NMR (200MHz, DMSO-d^6) 3.77 (3H, s), 7.23 (1H, t), 7.44-7.60 (3H, m), 7.78-7.92 (3H, m), 7.98-8.03 (2H, m), 8.43 (1H, d), 8.52 (1H, s), 10.52 (1H, s).

EXAMPLE 23

2-[3-(4-Chloro-2-methylphenylsulfamoyl)phenyl]benzoxazole-4-carboxylic acid methyl ester

Prepared from 3-(4-chloro-2-methylbenzenesulfonylamino)benzoic acid (190mg) and 2-hydroxyanthranilic acid methyl ester (100mg) to give the title compound (68mg) as an off-white solid.

TLC R_f 0.41 (50% ethyl acetate in hexane).

^{1}H NMR (200MHz, $CDCl_3$) 2.05 (3H, s), 4.10 (3H, s), 7.14-7.30 (3H, m), 7.53 (3H, t), 7.68 (1H, t), 7.83-7.89 (2H, m), 8.11 (1H, d), 8.61 (1H, d), 8.76 (1H, s).

EXAMPLE 24

2-[3-(4-Chloro-2-methylphenylsulfamoyl)phenyl]benzoxazole-7-carboxylic acid methyl ester

Prepared from 3-(4-chloro-2-methylbenzenesulfonylamino)benzoic acid (78mg) and 2-hydroxy-3-aminobenzoic acid methyl ester (78mg) to give the title compound (30mg) as a tan solid.

TLC R_f 0.54 (50% ethyl acetate in hexane).

^{1}H NMR (200MHz, $CDCl_3$) 2.07 (3H, s), 4.10 (3H, s), 6.63 (1H, bs), 7.12-7.27 (3H, m), 7.50 (1H, t), 7.65 (1H, t), 7.86 (1H, d), 8.00 (1H, d), 8.08 (1H, d), 8.53 (1H, d), 8.77 (1H, s).

EXAMPLE 25

N-(4-Bromophenyl)-3-(4-methylbenzoxazol-2-yl)benzenesulfonamide

Prepared from 3-(4-bromophenylsulfamoyl)benzoic acid (0.2g) and 2-amino-m-cresol (0.07g) to give the title compound (0.11g) as a white solid.

TLC R_f 0.87 (50% ethyl acetate in hexane).

^{1}H NMR (200MHz, DMSO-d^6) 2.60 (3H, s), 7.05 (2H, d), 7.20-7.50 (4H, m), 7.65 (1H, d), 7.80 (1H, t), 7.95 (1H, d), 8.40 (1H, d), 8.60 (1H, s).

EXAMPLE 26

3-(4-Nitrobenzoxazol-2-yl)-N-(4-trifluoromethylphenyl)benzene-sulfonamide

Prepared from 3-(4-trifluoromethylphenylsulfamoyl)benzoic acid (180mg) and 2-amino-3-nitrophenol (80mg) to give the title compound (27mg) as an off-white solid.

TLC R_f 0.44 (50% ethyl acetate in hexane).
^{1}H NMR (200MHz, DMSO-d^6) 7.35 (2H, d), 7.60 (2H, d), 7.80 (1H, t), 7.90 (1H, t), 8.10 (1H, d), 8.30 (2H, dd), 8.45 (1H, d), 8.6 (1H, s).

EXAMPLE 27

N-(4-Cyanophenyl)-3-(4-nitrobenzoxazol-2-yl)benzenesulfonamide

Prepared from 3-(4-cyanophenylsulfamoyl)benzoic acid (100mg) and 2-amino-3-nitrophenol (77mg) to give the title compound (50mg) as an off-white solid.

TLC R_f 0.28 (50% ethyl acetate in hexane).
^{1}H NMR (200MHz, $CDCl_3$) 7.35 (2H, d), 7.55-7.90 (4H, m), 8.00 (1H, d), 8.10 (1H, d), 8.30 (1H, d), 8.60 (1H, d), 8.95 (1H, s).

EXAMPLE 28

N-(4-Chloro-3-nitrophenyl)-3-(4-nitrobenzoxazol-2-yl)benzene-sulfonamide

Prepared from 3-(4-chloro-3-nitrophenylsulfamoyl)benzoic acid (100mg) and 2-amino-3-nitrophenol (77mg) to give the title compound (50mg) as an off-white solid.

TLC R_f 0.27 (50% ethyl acetate in hexane).
^{1}H NMR (200 MHz, $CDCl_3$) 7.30-7.45 (5H, m), 7.90-8.10 (3H, m), 8.30 (1H, d), 8.60 (1H, d), 8.95 (1H, s).

EXAMPLE 29

2-[3-(4-Trifluoromethylphenylsulfamoyl)phenyl]benzoxazole-7-carboxylic acid

A mixture of 3-(4-trifluoromethylphenylsulfamoyl)benzoic acid (100mg), methyl 3-aminosalicylate (48mg) and trimethylsilyl polyphosphate (1ml) in 1,2-dichlorobenzene (3ml) was heated at reflux under a nitrogen atmosphere for 3h. The mixture was allowed to cool and purified by column chromatography on silica, eluting with 5%-50% ethyl acetate in hexane to provide the methyl ester. The product was dissolved in methanol, filtered and concentrated *in vacuo*. A mixture of the methyl ester (40mg) and lithium hydroxide monohydrate (20mg) in tetrahydrofuran (3ml) and water (1ml) was stirred at 50° for 5h. The reaction mixture was allowed to cool and then partitioned between ethyl

acetate (10ml) and water (10ml). The aqueous phase was acidified with 2N hydrochloric acid and extracted with ethyl acetate (15ml). The organic phase was dried (magnesium sulfate) and concentrated *in vacuo* to give the title compound (21mg) as an off white solid.

TLC R_f 0.3 (50% ethyl acetate in hexane).

^{1}H NMR (200 MHz, DMSO-d^6) 7.30 (2H, d), 7.50 (1H, t), 7.60 (2H, d), 7.85 (1H, t), 8.00 (1H, d), 8.05 (1H, d), 8.15 (1H, d), 8.40 (1H, d), 8.60 (1H, s).

BIOLOGICAL ACTIVITY

The following assay can be used to demonstrate the activity of compounds according to the invention:

Measurement of Cyclic AMP PDE Activity

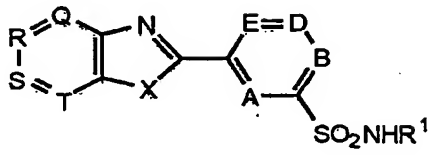
PDE7 hydrolyses cAMP to 5'-AMP, a linear nucleotide. The assay used to determine this activity is based on the observation that linear nucleotides bind preferentially to SPA yttrium silicate beads, compared to cyclic nucleotides, in the presence of zinc sulfate. The 5'-AMP, the product, therefore binds directly to the beads and cAMP does not. The binding of the radiolabelled product to the bead brings it into close enough proximity to allow tritium to excite the scintillant in the bead.

The PDE7 assay was carried out using Amersham Pharmacia SPA technology (Amersham Pharmacia Biotech). The assay was buffered with 50mM Tris containing 8.3mM $MgCl_2$ and 1.7mM EGTA pH 7.5. Assay buffer, inhibitor, cAMP (0.029μM, final) and 3H-cAMP (~5nM, final concentration) were pipetted into a 96 well microtitre plate. The reaction was initiated with the addition of 20μl of PDE7 enzyme [see Michaeli, T *et al.* (1993) J. Biol. Chem. 268, 12925-12932] to give a final volume of 100μl. The assay was incubated for 30 minutes at 30°. The reaction was terminated by the addition of 50μl SPA yttrium silicate beads. The plates were then sealed, mixed and counted on a Packard TopCount scintillation counter (Canberra Packard).

In this assay, compounds according to the invention have IC_{50} values of around 10μM and less, typically around 1μM and less.

CLAIMS

1. A compound of formula (1):



(1)

wherein

R^1 represents an aryl or heteroaryl group;

A, B, D and E, which may be the same or different, each represents a nitrogen atom or a $C(R^2)$ group [in which R^2 is a hydrogen or halogen atom or an alkyl, haloalkyl, alkoxy, haloalkoxy, hydroxy, $-NO_2$ or -CN group] provided that two or more of A, B, D and E are $C(R^2)$ groups;

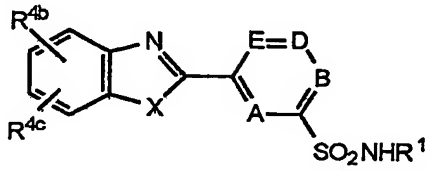
X represents an oxygen or sulphur atom or a $N(R^3)$ group in which R^3 is a hydrogen atom or an alkyl group;

Q, R, S and T, which may be the same or different each represents a nitrogen atom or a group $C(R^4)$ [in which R^4 is an atom or group $-L^1(Alk^1)_rL^2(R^5)_s$ in which L^1 and L^2, which may be the same or different, is each a covalent bond or a linker atom or group, r is zero or the integer 1, Alk^1 is an aliphatic or heteroaliphatic chain, s is an integer 1, 2 or 3 and R^5 is a hydrogen or halogen atom or a group selected from alkyl, $-OR^6$ [where R^6 is a hydrogen atom or an optionally substituted alkyl group], $-SR^6$, $-NR^6R^7$ [where R^7 is as just defined for R^6 and may be the same or different], $-NO_2$, -CN, $-CO_2R^6$, $-SO_3H$, $-S(O)R^6$, $-SO_2R^6$, $-OCO_2R^6$, $-CONR^6R^7$, $OCONR^6R^7$, $-CSNR^7R^7$, $-OCR^6$, $-OCOR^6$, $-N(R^6)COR^7$, $-N(R^6)CSR^7$, $S(O)NR^6R^7$, $-SO_2NR^6R^7$, $-N(R^6)SO_2R^7$, $-N(R^6)CON(R^7)(R^8)$ [where R^8 is a hydrogen atom or an optionally substituted alkyl group], $-N(R^6)CSN(R^7)R^8$), $-N(R^6)SO_2N(R^7)(R^8)$, $-C(R^6)=NO(R^7)$,cycloaliphatic, heterocycloaliphatic, aryl or heteroaryl group] provided that two or more of Q, R, S and T are $C(R^4)$ groups;

and the salts, solvates, hydrates and N-oxides thereof.

2. A compound according to Claim 1 wherein Q, R, S and T is each a $C(R^4)$ group.

3. A compound according to Claim 2 which has the formula (1a)



(1a)

wherein R^{4b} and R^{4c}, which may be the same or different, is each an atom or group $-L^1(Alk^1)_rL^2(R^5)_s$.

4. A compound according to Claim 3 wherein R^{4b} is a hydrogen, fluorine, chlorine or bromine atom or a $-CH_3$, $-OCH_3$, $-CF_3$, $-OCHF_2$, $-OCH_3$, $-CN$, $-CO_2H$, $-CO_2CH_3$, $-CO_2CH_2CH_3$, $-NO_2$, $-CONH_2$, $-CONHCH_3$, $-CONHCH_2CH_3$, $-CON(CH_3)_2$ or $-CON(CH_2CH_3)_2$ group.

5. A compound according to Claim 4 wherein R^{4a} is a hydrogen atom.

6. A compound according to Claim 1 to Claim 5 wherein A, B, D and E is each a $-C(R^2)$ group and R^2 is a hydrogen atom.

7. A compound according to Claim 1 to Claim 6 wherein R^1 is an optionally substituted phenyl, pyridyl or pyrimidinyl group.

8. A compound according to any of the preceding Claims wherein X is an oxygen atom or a NH group.

9. A compound which is
N-(4-Chlorophenyl)-3-(7-nitro-1H-benzimidazol-2-yl)benzene-sulfonamide;
N-(4-Cyanophenyl)-3-(7-nitro-1H-benzimidazol-2-yl)benzene-sulfonamide;

N-(3-Cyanophenyl)-3-(7-nitro-1H-benzimidazol-2-yl)benzene-sulfonamide;
N-(3,5-Dichlorophenyl)-3-(7-nitro-1H-benzimidazol-2-yl)benzene-sulfonamide;
N-(4-Bromo-2-chlorophenyl)-3-(7-nitro-1H-benzimidazol-2-yl)benzenesulfonamide;
N-Ethyl-4-[3-(7-nitro-1H-benzimidazol-2-yl)benzenesulfonylamino]-benzamide;
4-[3-(7-Nitro-1H-benzimidazol-2-yl)benzenesulfonylamino]benzoic acid ethyl ester;
N-(4-Chloro-2-methylphenyl)-3-(7-nitro-1H-benzimidazol-2-yl)-benzenesulfonamide;
2-[3-(2-Chlorophenylsulfamoyl)phenyl]-3H-benzimidazole-4-carboxylic acid methylester;
2-[3-(4-Chloro-2-methylphenylsulfamoyl)phenyl]-3H-benzimidazole-4-carboxylic acid;
2-[3-(5-Chloro-1H-benzimidazol-2-yl)benzenesulfonylamino]benzoic acid;
2-[3-(2-Chlorophenylsulfamoyl)phenyl]-3H-benzimidazole-4-carboxylic acid;
2-[3-(4-Chloro-2-methylphenylsulfamoyl)phenyl]benzoxazole-7-carboxylic acid;
2-[3-(5-Chlorobenzoxazol-2-yl)benzenesulfonylamino]benzoic acid;
2-[3-(4-Chloro-2-methylphenylsulfamoyl)phenyl]benzoxazole-4-carboxylic acid;
N-(4-Chloro-2-methylphenyl)-3-(4-nitrobenzoxazol-2-yl)benzene-sulfonamide;
N-(4-Bromophenyl)-3-(4-methylbenzoxazol-2-yl)benzenesulfonamide;
3-(4-Nitrobenzoxazol-2-yl)-N-(4-trifluoromethylphenyl)benzene-sulfonamide;
N-(4-Cyanophenyl)-3-(4-nitrobenzoxazol-2-yl)benzenesulfonamide;
N-(4-Chloro-3-nitrophenyl)-3-(4-nitrobenzoxazol-2-yl)benzene-sulfonamide; or
2-[3-(4-Trifluoromethylphenylsulfamoyl)phenyl]benzoxazole-7-carboxylic acid;
and the salts, solvates, hydrates and N-oxides thereof.

10. A pharmaceutical composition comprising a compound according to Claim 1 together with one or more pharmaceutically acceptable carriers, excipients or diluents.

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INTERNATIONAL SEARCH REPORT

ional Application No
PCT/GB 01/01479

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D235/18 C07D263/57 C07D277/66 A61K31/4184 A61K31/423 A61K31/428 A61P37/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
WPI Data, EPO-Internal, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 99 62905 A (ALMIRALL PRODESFARMA, S.A.) 9 December 1999 (1999-12-09) the whole document ---	1-10
A	WO 98 20007 A (DARWIN DISCOVERY LIMITED) 14 May 1998 (1998-05-14) the whole document --- -/--	1

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
22 June 2001	29/06/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Allard, M

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	MARTINEZ A ET AL: "Benzyl Derivatives of 2,1,3-Benzo- and Benzothieno'3,2-a!thiadiazine 2,2-Dioxides: First Phosphodiesterase 7 Inhibitors" JOURNAL OF MEDICINAL CHEMISTRY,AMERICAN CHEMICAL SOCIETY. WASHINGTON,US, vol. 43, 2 February 2000 (2000-02-02), pages 683-689, XP002166193 ISSN: 0022-2623 the whole document	1

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/GB 01/01479

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WO 9962905 A	09-12-1999	AU 4501199 A	20-12-1999
WO 9820007 A	14-05-1998	AU 711587 B	14-10-1999
		AU 4875897 A	29-05-1998
		EP 0946541 A	06-10-1999
		US 6069151 A	30-05-2000
		ZA 9710000 A	06-11-1998